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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/573,905 | 05/30/2006 | Michael Brines | WP03-1 A04-US | 2092 |

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| EXAMINER | |
|---|---|
| DEBERRY, REGINA M | |
| ART UNIT | PAPER NUMBER |
| 1647 | |
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| 11/24/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/573,905 | BRINES ET AL. | |
| | Examiner | Art Unit | |
| | Regina M. DeBerry | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,37-45 and 47-69* is/are pending in the application.

4a) Of the above claim(s) *1,37,38,40,49-55,57-66,68 and 69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39,41-45,47,48,56 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/29/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**Status of Application, Amendments and/or Claims**

The amendment, filed 13 November 2007, has been entered in full. Claim 1 was amended. Claims 2-36 were canceled. New claims 37-69 were entered.

Applicant's election with traverse of Group III (claims 39, 41-45, 47, 48, 56, 67) and species election of a chemically modified EPO having one or more modified lysine residues or a modification of the N-terminal amino group (i.e. claim 42 vii) and species election of mutated species S100E in the reply filed on 04 August 2008 is acknowledged. The traversal is on the grounds that Group IX (claim 68) determines whether a chemically modified or mutated EPO treats, prevents, delays the onset of, or reduces complications associated with adhesions by (1) inducing sepsis, adhesions or inflammation in a mammal; (2) administering the chemically modified or mutated EPO to the mammal; and (3) determining the adhesion score in the mammal to determine if less adhesions resulted from the administration of the chemically modified or mutated EPO. Applicant maintains that examining both Groups together would not impose an undue burden on the Examiner.

Applicant's arguments have been fully considered but are not found persuasive. Group III is drawn to a method of treating/preventing/delaying the onset of/reducing adhesion formation, abnormal fibrous band formation and formation of a connection between organs or scarring comprising administering an EPO to a subject. Group IX (claims 68 and 69) is drawn to a method for testing the ability of a modified EPO to treat/prevent/delay the onset of/reduce ***not only adhesion formation, but sepsis and***

***inflammation from infection, wherein sepsis, adhesion or a combination thereof*** **is induced in the mammal, comprising administering a modified EPO to said mammal**, then determining an adhesion score. Group III and Group IX are directed to methods that recite functionally distinct steps. In addition, the methods are drawn to treating different patient populations, which may or may not overlap. A search to identify documents relevant to the patentability of the claimed methods would not necessarily employ the same or similar search terms and techniques to identify relevant documents. As such, it would be burdensome to search the inventions of the Groups together. The requirement is still deemed proper and is therefore made FINAL.

Claims 1, 37, 38, 40, 49-55, 57-66, 68 and 69 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group, there being no allowable generic or linking claim. Election was made **with** traverse in the reply filed on 10 September 2007. Claims 39, 41-45, 47, 48, 56 and 67 are under examination. The claims will only be examined to the degree that they reflect the elected invention.

## Information Disclosure Statement

The information disclosure statement(s) (IDS) filed (29 July 2008) was received and complies with the provisions of 37 CFR §§1.97 and 1.98. There are 26 pages of references (A01-C402). They have been placed in the application file and the information referred to therein has been considered as to the merits. It noted that the IDS list various Office Actions and a patent interference. These references have been

considered by the Examiner, but will not be printed on the face of the patent issuing from this application.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39, 41-45, 47, 48, 56 and 67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method of **treating, delaying the onset of, or reducing** adhesion formation, abnormal fibrous band formation, formation of a connection between organs or scarring in a mammal, comprising administering to the mammal a therapeutically effective amount of **an erythropoietin (EPO) that is chemically modified at lysine residues or the N-terminal amino group, wherein said chemical modification is carbamylation at lysine residues or the N-terminal amino group** and a pharmaceutical acceptable carrier.

does not reasonably provide enablement for:

a method of **preventing** adhesion formation, abnormal fibrous band formation, formation of a connection between organs or scarring in a mammal, comprising administering to the mammal a therapeutically effective amount of **an unmodified EPO** (i.e. "**at least one erythropoietin (EPO) that is optionally** chemically modified or

mutated"; the Examiner understand "*optionally* chemically modified or mutated" to encompass EPOs that are unmodified**) or an EPO with any type of chemical modification or an EPO with any type of mutation** and a pharmaceutical acceptable carrier.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification teaches that carbamylated EPO does not retain erythropoietic activity and fails to bind with the classic homodimer EPO receptors, but advantageously maintains the tissue protective functionality of endogenous EPO (page 12, line 32-page 13, line 5). The specification teaches carbamylation of EPO via chemical modifications of the amino terminus or side chain of lysine (pages 13-14). The specification teaches variant EPOs wherein one or more sites in EPO have been mutated (page 14). The specification teaches S100E wherein the amino acid at position 100 has been changed to a glutamic acid (page 14, lines 15-16). The specification teaches the use of a rat abdominal sepsis model, wherein the animals are monitored for formation of adhesions (pages 29-30). A cumulative adhesion score is calculated for each animal 24 hours post-injury. Animals receiving carbamylated EPO had fewer adhesions than animals receiving saline (page 32 and page 34). The specification also teaches that animals receiving carbamylated EPO had a much higher survival rate and less scarring than animals receiving recombinant erythropoietin (rhEPO)(page 35).

The instant claims are not supported by an enabling disclosure for the following reasons:

The specification fails to teach the prevention of adhesion formation, abnormal fibrous band formation, formation of a connection between organs or scarring in a mammal upon EPO administration. Prevent means to completely stop a condition from occurring. "Prevention" is not a relative term, it is total. A very high degree of evidence is required, which is accepted in the art, that an absolute protection from the pathology exists over an extended period of time.

The specification fails to demonstrate that EPO with ***any type of chemical modification*** can treat, delay the onset of, or reduce adhesion formation, abnormal fibrous band formation, formation of a connection between organs or scarring in a mammal. Satake et al. (reference of record; Biochimica et Biophysica Acta, 1038:125-129, 1990) teach that modification of the positive charges of the lysine residues to neutral or negative charges, such as in acetylation, trinitrophenylation, carbamylation or succinylation cause a significant loss of recombinant human erythropoietin activity. ***However***, guanidination of amino groups of the lysine residues yielded derivatives that showed **higher biological activities** *in vitro* than native recombinant human EPO. Amidination of lysine residues had no effect on the activity. **The novelty of the instant is that the EPO does not retain erythropoietic activity (thus avoiding the risk of high hematocrit levels, thrombosis) but still has the tissue protective activity.** The art teaches that modifications in the EPO sequence are critical to the protein's

structure/function relationship. These modifications can either increase or decrease erythropoietic activity.

Furthermore, the specification fails to demonstrate that EPO with ***any type of EPO mutation (including those mutations EPO point mutations recited in claims 43-45)*** can treat, delay the onset of, or reduce adhesion formation, abnormal fibrous band formation, formation of a connection between organs or scarring in a mammal. The specification teaches variant EPOs wherein one or more sites in EPO have been mutated (page 14). The specification fails to teach the use of any of the recited mutant EPOs in a rat abdominal sepsis model, wherein the animals are monitored for the formation of adhesions and cumulative adhesion scores are calculated. Yasuda et al. (US 7,300,916 B2) *teach the treatment of scars using EPO antagonists* (abstract, column 1, lines 1-16; column 3, lines 1-36; column 6, line 60-column 7, line 36 and claims). Yasuda et al. teach that EPO receptor proteins and anti-EPO antibodies bind to EPO to block binding of EPO to an EPO receptor. Thus, the Yasuda data teaches the use of EPO antagonist for scar treatment versus the instant application which teaches the use of EPO for scar treatment. An EPO with any type of mutation (including those mutations EPO point mutations recited in claims 43-45) could act as antagonists and/or have the opposite effect of the claimed activity. The mutant EPOs could retain erythropoietic activity and bind the classic homodimer EPO receptors. Conceivably, the mutant EPOs could fail to bind the classic homodimer EPO receptors, but still lack the biological activity of treating, delaying the onset of, or reducing adhesion formation, abnormal fibrous band formation, formation of a connection between organs or scarring

in a mammal. It is known for proteins that even a single amino acid change/mutation can destroy or affect the function of the biomolecule. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. It would require an indeterminate quantity of fundamentally unpredictable investigational experimentation of the skilled artisan to determine whether any mutant modifications of EPO, as encompassed by the claims, could be used in an *in vivo* manner (i.e. treating adhesion formation, scarring, etc) in a mammal, wherein said EPO lacks or is diminished of erythropoietic activity (i.e. increase in hemoglobin concentration, hematocrit or thrombosis).

Lastly, the instant claims recite the limitation, **"..at least one** erythropoietin (EPO) that **is optionally** chemically modified or mutated..". This limitation encompasses EPOs that are unmodified. The specification fails to demonstrate that unmodified EPO can treat, delay the onset of, or reduce adhesion formation, abnormal fibrous band formation, formation of a connection between organs or scarring in a mammal. Example 3 from the instant specification clearly demonstrates that animals receiving carbamylated EPO had a much higher survival rate and less scarring than animals receiving recombinant erythropoietin (rhEPO; i.e. unmodified).

Due to the large quantity of experimentation necessary to show that the onset of the claimed condition has been prevented; the large quantity of experimentation necessary to make an EPO with any type of chemical modification or any type of mutation; the large quantity of experimentation necessary to demonstrate that an EPO with any type of chemical modification or any type of mutation can be employed an *in*

*vivo* manner (for treating adhesion formation, scarring, etc) in a mammal, wherein said EPO lacks or is diminished of erythropoietic activity; the lack of direction/guidance presented in the specification regarding same; the absence of working examples; the complex nature of the invention; the contradictory state of the prior art which teaches that EPO antagonists can be used to treat scars (see Yasuda et al.), the unpredictability of the effects of chemical modifications on EPO function (see Sataka et al.), and the breadth of the claims which fail to recite limitations regarding chemical modifications and mutations in EPO, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

## ***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marianne P. Allen/
Primary Examiner, Art Unit 1647

/R. M. D./
Examiner, Art Unit 1647
11/17/08